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**Initial treatment of steroid-sensitive idiopathic nephrotic syndrome in children with mycophenolate mofetil vs. prednisone:
A randomized, controlled, multicenter trial (INTENT Study)**

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1 Initial treatment of steroid-sensitive idiopathic nephrotic syndrome in children with mycophenolate
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5 mofetil vs. prednisone:
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7 A randomized, controlled, multicenter trial (INTENT Study)
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105 **Abstract**

106 **Introduction**

107 Idiopathic nephrotic syndrome is the commonest glomerular disease in childhood with an incidence
108 of 1.8 cases per 100.000 children in Germany. The treatment of the first episode implies two aspects:
109 induction of remission and sustainment of remission. The recent KDIGO, American Academy of
110 Pediatrics (AAP) and German guidelines for the initial treatment of the first episode of a nephrotic
111 syndrome recommend a 12-week-course of prednisone. Even though being effective, this treatment
112 is associated with pronounced glucocorticoid-associated toxicity due to high-dose prednisone
113 administration over a prolonged period of time. The aim of the INTENT study is to show that an
114 alternative treatment regimen with mycophenolic acid is not inferior regarding sustainment of
115 remission but with lower toxicity compared to treatment with glucocorticoids only.

116 **Methods and design**

117 The study is designed as an open, randomized, controlled, multicenter trial. 340 children with a first
118 episode of steroid-sensitive nephrotic syndrome and achieved remission by a standard prednisone
119 regime will be enrolled in the trial and randomized to one of two treatment arms. The standard care
120 group will be treated with prednisone for a total of 12 weeks; in the experimental group the
121 treatment is switched to mycophenolate mofetil, also for a total of 12 weeks treatment duration. The
122 primary endpoint is the occurrence of a treated relapse within 24 months after completion of initial
123 treatment. This study is funded by the German Federal Ministry of Education and Research.

124 **Ethics and dissemination**

125 Ethics approval for this trial was granted by the ethics committee of the Medical Faculty of the
126 University of Heidelberg (AFmu-554/2014). The study results will be published in accordance with the
127 CONSORT statement and SPIRIT guidelines. Our findings will be submitted to major international
128 pediatric nephrology and general pediatric conferences and submitted for publication in a peer-
129 reviewed open access journal.

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Trial registration: European Clinical Trials Database EudraCT No.: 2014-001991-76

Date of registration: October 30, 2014

Deutsches Register Klinischer Studien – German clinical trials register

DRKS00006547

Date of registration: Februar 24, 2017

Keywords: Mycophenolat mofetil; steroid-sensitive nephrotic syndrome, steroids, alternative treatment

Article summary

Strengths and limitations of this study

- This is the first trial worldwide that prospectively evaluates a steroid-reduced initial treatment alternative for childhood nephrotic syndrome
- This trial has the potential to reduce steroid-associated side effects without losing efficacy
- If our hypotheses turn out to be true, the experimental therapy has the potential to become the future standard of care
- This is one of the few randomized, controlled, prospective, multicenter trials in pediatric nephrology, but due to clinical and financial aspects the trial is not blinded

Word count: 5688 words

157 Introduction

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159 Idiopathic nephrotic syndrome in childhood

160

161 *Clinical course and epidemiology*

162 Idiopathic nephrotic syndrome in childhood, defined as the combination of heavy proteinuria
163 ($>40 \text{ mg/m}^2$ body surface area (BSA) per h) and hypalbuminemia ($<25 \text{ g/L}$), in general accompanied
164 by edema and hyperlipidemia, is a rare, relapsing disease with an incidence of 1.8 per 100.000
165 children below 16 years of age in Germany (German registry of rare pediatric diseases, ESPED 2005-
166 2006), resulting in an annual rate of 200-250 new patients.[1] The classification according to the four
167 following categories is important for diagnostics, treatment and prognosis of nephrotic syndrome in
168 childhood: etiology, age at onset, histology, response to glucocorticoids. The primary idiopathic
169 nephrotic syndrome with a typical onset at 1-10 years of age should be differentiated from
170 patients with secondary causes or patients with age at onset younger than one year (congenital
171 and infantile forms) or older than 10 years of age. Approximately 80% of the children with
172 idiopathic nephrotic syndrome have minimal change disease in renal biopsy and approximately 7%
173 focal segmental glomerulosclerosis. The most important prognostic factor is steroid-sensitivity
174 occurring in over 90% of the patients.

175

176 *Treatment*

177 The treatment of the first episode implies two aspects: induction of remission and sustainment
178 of remission. The *Gesellschaft für Pädiatrische Nephrologie (GPN)*, formerly known as
179 *Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)*, defined the standard
180 of care for children with nephrotic syndrome.[2–7] *The effectual guideline for the initial*
181 *treatment of the first episode of a nephrotic syndrome recommends in detail: 60 mg*

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182 *prednisone/m² BSA per day (maximum 80 mg/day) for 6 weeks followed by alternate day prednisone*
183 *40 mg/m² BSA (maximum 60 mg/48 hours) for another 6 weeks.[8]*
184 In case of steroid-sensitivity remission usually occurs within 7-14 days of
185 treatment; the overall duration of initial prednisone treatment is 12 weeks in order to sustain
186 remission. This regimen is associated with a relapse rate of 51% within 24 months after initial
187 prednisone
188 therapy, and a rate of frequent relapses (definition: relapses occur 4 or more times in any 12 month
189 period or 2 or more relapses within the first 6 months period after initial response) of 29% is
190 expected.

191
192 **Side effects of treatment**

193 Even though being effective, this treatment is associated with pronounced glucocorticoid associated
194 toxicity due to high-dose prednisone administration over a prolonged period of time.
195 The major side effects, which have been shown consistently in previous studies,[3, 4, 9]
196 comprise obesity, striae, hypertrichosis, cataract, glaucoma, arterial hypertension, psychological
197 disturbances, growth failure, disturbances in carbohydrate and lipid metabolism, osteopenia,
198 and avascular bone necrosis. Not all of these side effects are completely reversible after cessation of
199 steroid therapy. In one study for example, excessive gain of weight during initial steroid therapy
200 persisted in a significant subset (47%) of patients following cessation of glucocorticoid therapy.[10]
201 Obesity following cessation of glucocorticoid therapy was associated with
202 hyperlipidemia, which might enhance the cardiovascular risk of these patients in the long run.[11]
203 Other studies have shown that exposure to higher doses of glucocorticoids in the initial therapy leads
204 to more toxicity without prevention of future relapses.[12–15]

205
206 **Role of mycophenolate mofetil in the treatment of nephrotic syndrome in childhood**

207 Mycophenolate mofetil (MMF), the pro-drug of its active moiety mycophenolic acid (MPA), is a

208 potent, selective and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH),
209 the key enzyme of *de novo* purine synthesis in activated lymphocytes. MMF is
210 effective in sustaining remission in patients with frequently relapsing or glucocorticoid-dependent
211 nephrotic syndrome.
212 Four prospective studies in patients with frequently relapsing or glucocorticoid-dependent nephrotic
213 syndrome receiving a long-term therapy with MMF explored the possibility of withdrawing
214 prednisone, which was successful in >50% of patients without further relapses.[16–19]
215 In children with glucocorticoid-dependent nephrotic syndrome on MMF, Dorresteijn et al. reported
216 relapse rates of 25% after 6 months and 45% after 12 months, respectively.[20] In a phase II Bayesian
217 trial, Baudouin et al. confirmed the effect of MMF in reducing relapse rates and in sparing
218 glucocorticoids in children with glucocorticoid-dependent nephrotic syndrome.[21] A recent GPN
219 study on the maintenance of remission in children with frequently relapsing or steroid-dependent
220 nephrotic syndrome has shown that MMF in adequate exposure is as effective as cyclosporine A
221 (CSA) in sustaining remission without the burden of CSA-induced nephrotoxicity.[22]
222
223 So far, no studies with MMF for the initial treatment of the steroid-sensitive
224 nephrotic syndrome (SSNS) in children have been performed. However, it seems coherent to use the
225 efficacy of MMF also for sustaining remission in the initial treatment of SSNS and to benefit from its
226 lower toxicity compared to glucocorticoids.

228 Rationale

229 The initial treatment of the idiopathic nephrotic syndrome in children requires sufficient
230 immunosuppressive therapy, but should avoid toxicity, since the intensity of the initial treatment
231 does not influence the long-term course of the disease. For example, a GPN trial on the initial
232 treatment of nephrotic syndrome revealed no overall advantage of an intensified

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3 233 immunosuppressive protocol adding CSA in terms of occurrence of relapses during a follow-up of 24
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5 234 months.[5, 12, 13]
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7 235 Our hypothesized novel treatment protocol has the potential to reduce the burden of glucocorticoid-
8
9 236 associated side effects and associated cardiovascular risk factors, if the novel protocol is not inferior
10
11 237 to the standard therapy regarding sustainment of remission. If our hypothesis turns out to be true,
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13 238 this novel therapy has the potential to become the standard of care for the initial treatment of SSNS
14
15 239 in children.

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20 241 **Methods/design**

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22 242 **Aim**

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24 243 The main purpose of the study is to show that MMF in the initial treatment of SSNS in children is not
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26 244 inferior regarding maintenance of initial remission and subsequent relapse rate compared to the
27
28 245 standard prednisone regimen.

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32 247 **Study design**

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34 248 This is a prospective, randomized, multicenter, controlled, open, parallel group phase III non-
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36 249 inferiority trial.

37
38 250 After initiation of the study, patients will be screened consecutively and eligible patients will be
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40 251 enrolled into the study at each center.

41
42 252 Each sites' principal investigator has to declare to the coordinating investigator/sponsor that
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44 253 he/she will conduct the study according to the protocol, ethical rules, and to provide the support
45
46 254 as needed. To minimize a potential performance bias, this will be fixed in a contract prior to
47
48 255 commencing the study. The clinical monitor will introduce the sites in detail to study procedures
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50 256 and documentation in advance.

51
52 257 Bias by potential influential factors will be addressed by inclusion as covariates into the
53
54 258 statistical analysis. Independent clinical on-site monitoring to ensure patients safety and

integrity of the clinical data in adherence to study protocol will focus on source data documentation, correctness of data, and adherence to study procedures, e.g. randomization and treatment.

Based on the performed interventions and planned analysis blinding is not feasible to minimize bias, because the interventions can easily be differentiated due to visible side effects such as obesity, which is only expected in the standard care group. Furthermore, MMF is used in liquid form as a suspension and prednisone as a tablet. However, the primary endpoint is based on standardized diagnostic work-up results, i.e. objective criteria.

The duration of the study for each subject is expected to be 27 months (including 24 months follow-up after intervention). (Figure 1 and Figure 2)

Patient and public involvement

Patients were not directly involved in the study development and design. Repeated discussions with patient representatives beforehand showed one of their main wishes that is reduction of steroids in the treatment of nephrotic syndrome.

We generated an information document for parents in form of a flyer that was distributed also to patient initiatives. Spreading out information on the study shall improve recruitment. There is no patient adviser involved in the conduct of the study, neither was the burden of the intervention assessed by patients or their parents during study development.

Study results will be published open access. Patients and their representatives will be informed through meetings and a brief summary of the results distributed by local investigators.

Recruitment

The study is conducted on a multicenter basis. The rarity of the disease requires a nationwide recruitment. The planned 35 study centers are evenly distributed over

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2
3 284 Germany. Each study center is coordinating a number of collaborating hospitals and practitioners
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5 285 that will transfer eligible patients with primary onset steroid-sensitive nephrotic syndrome for
6
7 286 screening, enrollment, randomization and study visits. 400 patients should be assessed for eligibility,
8
9 287 340 subjects should be enrolled in the clinical study, i.e. 170 subjects per treatment group.
10

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13 289 **Inclusion criteria and exclusion criteria**

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15 290 ***Inclusion criteria***

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17 291 Subjects meeting all of the following criteria will be considered for admission to the study:

- 18
19 292 - First episode of SSNS
20
21 293 - *Remission induced by prednisone or prednisolone 60 mg/m² BSA (maximum 80 mg/day) per day*
22
23 294 *within 28 days*
24
25 295 - Male and female children aged ≥ 1 year and ≤ 10 years at beginning of the study (typical
26
27 296 age range of patients with SSNS)
28
29 297 - Ability of the persons having care and custody of the child to understand character
30
31 298 and individual consequences of clinical study
32
33 299 - Written informed consent of the persons having care and custody of the child (must
34
35 300 be available before enrollment in the study)
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37 301

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39 302

40 302 ***Exclusion criteria***

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42 303 Subjects presenting with any of the following criteria will not be included in the study:

- 43
44 304 - Secondary nephrotic syndrome
45
46 305 - Estimated glomerular filtration rate (eGFR) <90 mL/min x 1.73 m² BSA
47
48 306 - Ongoing treatment with systematically administered glucocorticoids or other
49
50 307 immunosuppressive drugs at time of first episode of nephrotic syndrome
51
52 308 - Hemoglobin concentration of ≤90 g/L (SI unit)
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54 309 - Leucocyte count of ≤2.5 x 10⁹/L (SI unit)
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3 310 - Severe chronic gastrointestinal disease
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5 311 - History of hypersensitivity to MMF or to any drug with similar
6
7 312 chemical structure or to any excipient present in the pharmaceutical form of
8
9 313 suspension of MMF (CellCept® suspension)
10
11 314 - Refusal of subject
12
13 315 - Participation in other clinical studies or observation period of competing studies
14
15 316

17 317 **Study medication**

18
19 318 The sponsor, i.e. the University Hospital Heidelberg, will provide the required study medication
20
21 319 (mycophenolate mofetil, CellCept® suspension). Careful records will be kept of the study medication
22
23 320 supplied to the centers and distributed to the patients.
24
25 321 Prednisone is used as standard therapy following the definition of the *GPN* (standard treatment) and
26
27 322 is prescribed as usual.
28
29

- 30 323
31
32 324 • Prednisone or prednisolone (control intervention)
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36 326 • MMF is administered in liquid form (CellCept® suspension (Roche Registration Ltd.))
37
38 327 (experimental intervention)
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42 329 **Adherence**

43
44 330 Adherence will be recorded by the patients' diary.
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48 332 **Screening**

49
50 333 All patients who seem suitable for study participation and take part in the screening will receive a
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52 334 screening number and will be registered in a screening log. Together with the center ID this will be
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54 335 the unique identification number throughout the study.
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336 Parents of children with initial episode of idiopathic nephrotic syndrome aged between 1 and 10
337 years and treated with standard regime (prednisone 60 mg/m² BSA per day) will be informed about
338 the ongoing INTENT study. If the child fulfills the inclusion criteria the persons having care and
339 custody of the child and the patient, if ≥6 years of age, will be formally elucidated about the INTENT
340 study by the study center in a form understandable to him or her and asked for written
341 assent/consent.

342
343 For checking the exclusion criteria concerning eGFR, leucocyte count and hemoglobin concentration
344 the most recent lab values should be used; they should have been obtained no more than 28 days
345 prior to visit 1.

346
347 **Randomization**

348 To achieve comparable intervention groups, patients will be allocated in a concealed fashion by
349 means of randomization using a centralized web-based tool (www.randomizer.at). Randomization
350 will be performed stratified by age groups (grouped: <7 years of age, ≥7 years of age), because age is
351 known to influence the occurrence of relapses. If the randomizer is not available in urgent cases the
352 Institute of Medical Biometry and Informatics can be contacted and a biometrician or data manager
353 will perform the randomization.

354
355 **Intervention**

356 Maximum duration of treatment is 12 weeks after first day of initial treatment of SSNS. (Figure 1)

357
358 **Control intervention**

- 359 • Prednisone, which is continued for a total of 6 weeks with the dosage of 60 mg/m²
360 BSA/d (maximum 80 mg), is given twice per day or three times per day

362 plus

363

364 • Prednisone, which is given for another total of 6 weeks with the dosage of 40 mg/m²

365 BSA (maximum 60 mg) on alternate days (every other day) in one dose in the

366 morning

367

368 Resorption of prednisone is independent of food intake.

369

370 **Experimental intervention**

371 • MMF is given in a dosage of 1200 mg/m² BSA/d as a

372 suspension (200 mg/mL) until 12 weeks total treatment duration. MMF is given twice a

373 day, i.e. every 12 hours (± one hour)

374 • The suspension of MMF is prepared in the study center (according to the

375 summary of product information)

376 • The persons having care and custody of the child are informed that MMF should be

377 given 30 minutes before or 60 minutes after food intake.

378 • For the first two weeks from randomization on, prednisone is given with the dosage

379 of 40 mg/m² BSA (maximum 60 mg) on alternate days (every other day) in one dose in

380 the morning.

381 • *At Visits 2 and 3 MPA-exposure is measured by a limited sampling strategy (blood samples are*

382 *obtained at time points 0, 1 and 2 hours after intake of MMF*

383

384 **Recording of primary endpoint**

385 Daily dipstick testing of urine (Albustix®) and documentation in a standardized diary by a person

386 having care and custody of the child is common current practice in the care of patients with

387 nephrotic syndrome in pediatric nephrology centers.

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3 388 No guideline exists on whether standard relapse treatment with prednisone should be started
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5 389 immediately when definition of relapse is fulfilled to avoid the associated complications of an
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7 390 edematous relapse or whether treatment should be delayed for several days to determine whether
8
9 391 proteinuria resolves spontaneously. Therefore, in the INTENT study a time period of up to 10 days is
10
11 392 allowed for a possible spontaneous remission, before standard therapy for relapse is started.
12
13 393 Treatment of a relapse has to be performed according to standard therapy of the *GPN*. Relapses with
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15 394 and without treatment are documented in the eCRF.
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17 395 Treatment of frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome
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19 396 with other medications than prednisone is carried out according to center practice, because there is
20
21 397 no internationally accepted guideline on this topic. The performed treatment with
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23 398 immunosuppressive agents such as CSA, tacrolimus, MMF, cyclophosphamide, rituximab, or
24
25 399 levamisole is documented in the eCRF.
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28 400 After completion of the study, patients will be treated according to center practice.
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32 402 **Outcome measures**

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34 403 **Primary study endpoint**

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36 404 The primary efficacy endpoint is occurrence of a treated relapse within 24 months after completion
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38 405 of initial treatment. The rationale is that this endpoint was chosen in all previous studies on the initial
39
40 406 treatment of SSNS in children and is also the primary endpoint in various meta-analyses on this
41
42 407 topic.[3–5, 7, 8]
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45 408 Definition of relapse: Relapse is denoted by a reappearance of proteinuria for 3 consecutive days:

46
47 409 Albustix® ≥2+ (first or second morning urine)

48
49 410 or

50
51 411 urine protein/creatinine (Up/c) ratio ≥2 g/g (first or second morning urine)

52
53 412 or

54
55 413 urine protein excretion of ≥40mg/m² BSA/h (urine collection for minimum 12 hours)
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414

415 Relapses with and without treatment are documented. The primary endpoint is fulfilled by the first
 416 treated relapse.

417

418 **Secondary endpoints**

419 Secondary endpoints are divided into five items:

420 1. Course of the disease as described by the following criteria

421 a. Time from remission to first relapse

422 b. Number of relapses during follow-up

423 c. Mean relapse rate per patient and year

424 d. Number of frequent relapsers

425 e. Time from remission to intensification of immunosuppressive treatment with other
 426 drugs due to glucocorticoid-induced toxicity

427 f. Rate of patients who require more intense immunosuppressive treatment

428 2. Glucocorticoid-associated toxicity:

429 a. Cumulative prednisone dose as mg/m²

430 b. As there is no validated score for glucocorticoid-induced toxicity, each item is
 431 registered separately. At study visits 1-8, body mass index, blood pressure, and
 432 growth will be checked for quantitative influence, striae, hypertrichosis, acne, and
 433 psychological disturbances by yes or no for qualitative influence. Additionally, at
 434 study visits 1, 5, and 8, patients will be checked for cataract and glaucoma (by yes or
 435 no).

436 3. MMF-associated toxicity: At all visits, patients will be checked for known side effects of MMF,
 437 especially diarrhea, blood cell count disturbance, and infections.

438 4. Health-related quality of life, which may be impaired in children with nephrotic syndrome
 439 will be measured with a validated questionnaire (DISABKIDS) at visits 1/5/8.

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5. Days missing school attendance and days of hospitalization will be documented as a measure for the impact of the disease on everyday life.

It is expected that the MMF-based regimen will avoid acute and long-term glucocorticoid-associated toxicity and is therefore superior regarding the benefit/risk ratio. However, this will not be tested confirmatorily, since there is no endpoint or score summarizing the different aspects of side effects.

Statistical considerations

Sample size calculation

The sample size calculation is based on the primary efficacy endpoint “occurrence of a treated relapse within 24 months after completion of the initial treatment”. In the literature varying information is given regarding the relapse rate for the control group receiving standard prednisone therapy. We have decided to assume a relapse rate of 51% according to Gipson et al.[8] The same rate is expected for the experimental group. If the relapse rate in the experimental group accounts to less than 15% above the relapse rate of the control group, this will be considered as clinically irrelevant based upon clinical judgement. Therefore the margin is set to $\delta=0.15$. As the direction of the difference to be established is known for non-inferiority studies and as - due to the rareness of the disease and the related limited available number of patients - the study could otherwise not be performed with sufficient power, a one-sided significance level of 5% is applied. Testing at a one-sided significance level of $\alpha = 5\%$ and aspiring a power of 80%, a total of 272 patients (136 per group) are required (calculations performed with ADDPLAN 6.0). To account for a 10% drop-out rate and major protocol violations in a further 10%, 340 patients will be randomized.

Adherence/Rate of loss of follow up

The nephrotic syndrome in children is mostly an acutely presenting disease, and parents are very concerned about their child. With standard prednisone treatment we observe a high adherence to therapy. According to our previous experience in performing studies in pediatric nephrology we assume that a minimum of 85% of patients assessed for eligibility will be allocated to the study [4, 5, 22]. Due to the exclusive care of these patients in specialized pediatric nephrology centers we calculate with a loss of follow-up either due to drop-out or major protocol violation of maximum 20% which corresponds to our previous studies.[4, 5, 22] The recent study of the GPN, showing that MMF is efficacious in sustaining remission in children with frequently relapsing nephrotic syndrome, had only a drop-out rate of 4%. Therefore, for the entire study, we estimated 400 children with steroid-sensitive nephrotic syndrome to be assessed for eligibility, 340 to be allocated to study and 272 patients to be analyzed per protocol. However, in cases of premature withdrawal by a patient the persons having care and custody of this patient will be asked for informed consent so that routinely recorded data by the covering physician can be used for the INTENT study. In this manner as many data as possible is recorded for evaluation of treatments in this rare disease.

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480 ***Analysis populations***

The primary analysis will be performed for both the per-protocol population (PP) and the intention-to-treat population (ITT). The PP population comprises all patients, who were treated according to the randomized treatment as outlined in the protocol without major protocol violations (e.g., reduction of study medication of >50% or interruption of study medication of >3 days, violation of inclusion or exclusion criteria). The ITT population will comprise all patients randomized into the study. In this set, every patient is analyzed according to the group randomized into.

Since there may be patients who withdraw from the study after the treatment period or within the treatment period but consent to the analysis of routinely recorded data was given the inclusion of these patients into the ITT population will be decided case by case before database lock and defined when writing the statistical analysis plan (SAP). As appropriate, a third population will be defined for

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analysis of the primary and important secondary endpoints. How to deal with these patients and their data in detail depends on the time point of withdrawal and the amount and reliability of the routinely collected data.

The safety set will comprise all patients who have received study medication at least once, and will allocate the patients to the treatment they actually received, regardless of randomization. Whether routinely collected data of patients who withdraw prematurely can be included herein depends on the reliability of the collected safety data.

Statistical methods

The non-inferiority of the experimental group vs. control group will be evaluated using the test according to Farrington and Manning. The one-sided significance level is set to 5%.

The hypotheses to be assessed in the primary efficacy analysis are formulated as follows:

$H_0: p_{\text{MMF}} - p_{\text{Prednisone}} \geq \delta$ ($\delta=0.15$, non-inferiority margin, see sample size calculation for justification)

$H_1: p_{\text{MMF}} - p_{\text{Prednisone}} < \delta$, where p_* denotes the relapse rate in the respective group.

Before database closure the assignment of patients to the PP population (patients with no major protocol violations) and the ITT population (as classified by the intent-to-treat principle) are defined in the statistical analysis plan. The confirmatory analysis is performed for both the PP population and the ITT population. This approach reflects the equal importance of both analysis sets in a non-inferiority trial. For the PP analysis missing values for the primary endpoint are not expected. In the ITT population missing values will be replaced according to Higgins.[23] As appropriate, a third population will be defined to adequately incorporate routinely collected data of patients who withdraw prematurely but gave informed consent for usage of routinely collected data. Details on inclusion of such data into sensitivity analyses of primary and secondary endpoints will be defined in

517 more detail in the SAP. In case of uncertainty regarding data quality and reliability these patients will
518 only be analyzed descriptively.

519 Additionally, binary logistic regression models will be performed as sensitivity analysis for the
520 intervention comparison of the relapse rates adjusting for age, gender, center (grouped), and for
521 results of therapeutic drug monitoring (grouped) based on different populations (PP, ITT, with values
522 of drop-outs set to worst case).

523 All secondary outcomes will be evaluated descriptively, using appropriate statistical methods based
524 on the underlying distribution of the data. Descriptive p-values are reported together with 95%
525 confidence intervals for the corresponding effects. Descriptive statistics for continuous parameters
526 and scores include number of non-missing observations, mean, standard deviation, median,
527 minimum and maximum, performed for treatment groups as well as subgroups and overall. The
528 description of categorical variables (ordinal or nominal) includes the number and percentage of
529 patients belonging to the relevant categories in the study population as well as to each treatment
530 group.

531 Rates of adverse and serious adverse events will be calculated with 95% confidence intervals for
532 treatment group comparisons.

533 Statistical methods are used to assess the quality of the data, homogeneity of treatment groups,
534 endpoints and safety of the two intervention groups. Details of the statistical analysis will be fixed at
535 the latest in the SAP to be prepared within the first year after start of patient recruitment. All
536 persons taking part in the preparation of the SAP and possible later changes to it will only have
537 access to blinded data to avoid introduction of bias.

538

539 **Interim Analyses**

540 No interim analysis will be performed for the following reason: The recruitment phase is planned to
541 be 36 months. The primary endpoint is occurrence of treated relapse within 24 months after end of
542 initial treatment. Therefore, information on the primary endpoint for a first portion of the study

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543 patients will be available not before end of the recruitment phase. For this reason, a group-
544 sequential approach was not pursued.
545 However, an independent data safety monitoring board (DSMB) will closely monitor the recruitment,
546 the reported adverse events, the data quality of the study and the occurrence of potential early
547 relapses during the intake of MMF, thus ensuring the ethical conduct of the study and protecting the
548 safety interests of patients.

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550 **Adverse events**

551 Adverse events (AEs) will be ascertained by the investigators using non-leading questions,
552 noted as spontaneously reported by the patients to the medical staff or observed during any
553 measurements on all study days. The observation period begins with the first administration of
554 the Investigational Medicinal Product and ends with visit 4, (i.e. 6 months after day 1 [= first day of
555 treatment with standard therapy]). The patient or his primary care physician should report any AE
556 during the outpatient period via phone to the investigator.
557 AEs will be documented in the patient file and in the electronic case report form (eCRF). All subjects
558 who present AEs,
559 whether considered associated with the use of the study medication or not, will be monitored by
560 the responsible investigator to determine their outcome; this applies to withdrawals, too.

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562 All serious adverse events (SAEs) and their relevance for the benefit/risk assessment of the study will
563 be evaluated continuously during the study and for the final report.

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565 All SAEs must be reported by the investigator to the Department of Pharmacovigilance at the
566 Coordination Center for Clinical Trials (KKS) Heidelberg within 24 hours after the SAE becomes known
567 using the "Serious Adverse Event" form.

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3 569 Suspected unexpected serious adverse events (SUSARs) are to be reported to the responsible ethics
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5 570 committee, the competent authority and to all participating investigators within defined timelines,
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7 571 i.e. they are subject to an expedited reporting.

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9 572 All SAEs will be subject to a second assessment by a designated person or his deputy, who will be
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11 573 independent from the reporting investigator.

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15 575 **Data management**

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17 576 ***Data management and quality assurance***

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19 577 The investigator or a designated representative must enter all protocol-required information in the
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21 578 eCRF. The eCRF should be completed as soon as possible after the information is collected,
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23 579 preferably on the same day when a study subject is seen for an examination, treatment, or any other
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25 580 study procedure. The reason for missing data should be provided. The investigator is responsible for
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27 581 ensuring that all sections of the eCRF are completed correctly and that entries can be verified in
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29 582 accordance with the source data. Any entry and correction in the Remote Data Entry System will be
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31 583 documented automatically in an audit file.

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33 584 Completeness, validity and plausibility of data will be checked in time of data entry (edit-checks) and
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35 585 using validating programs, which will generate queries. The investigator or the designated
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37 586 representatives are obliged to clarify or explain the queries. If no further corrections are to be made
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39 587 in the database it will be closed and used for statistical analysis. All data management procedures
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41 588 will be carried out on validated systems and according to the current Standard Operating Procedures
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43 589 (SOPs) of the Institute of Medical Biometry and Informatics (IMBI) of the University of Heidelberg.
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49 591 **Ethical and Legal Aspects**

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51 592 The procedures set out in this study protocol, pertaining to the conduct, evaluation, and
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53 593 documentation of this study, are designed to ensure that all persons involved in the study abide by
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55 594 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human
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3 595 Use harmonized tripartite guideline on Good Clinical Practice (ICH-GCP) and the ethical principles
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5 596 described in the applicable version of the Declaration of Helsinki.
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7 597 The study will be carried out in conformity with the ICH Topic E6, Guideline for Good Clinical Practice,
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9 598 including post Step 4 errata, September 1997, Directive 2001/20/EC (April 4, 2001), Commission
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11 599 Directive 2005/28/EC (April 8, 2005), National regulatory requirements/guidelines of the
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13 600 participating countries concerning Clinical Studies [e.g. federal drug law (AMG), GCP ordinance (GCP-
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15 601 Verordnung), Medical device law (MPG)], general national regulatory requirements, e.g.
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17 602 Bundesdatenschutzgesetz (BDSG).
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23 605 **Ethics committee approval**

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26 606 Ethical approval of the INTENT study was granted by the ethics committee of the Medical Faculty of
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28 607 the University of Heidelberg (AFmu-554/2014) on March 18, 2015. This approval has subsequently
29
30 608 been confirmed by the local ethics committees of all participating centers. A list of all local ethics
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32 609 committees and all participating centers is provided as an additional file.

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34 610 The latest version of the trial protocol (version 5.0) was approved by the ethics committee on June
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36 611 01, 2016.

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40 613 **Approval of the regulatory authorities**

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42 614 According to the German Federal law the study was approved by the Federal Institute of Drugs and
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44 615 Medical Devices on April 02, 2015 (reference number 61-3910-4040246). The latest version of the
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46 616 trial protocol (version 5.0) was approved by the Federal Institute of Drugs and Medical Devices on
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48 617 July 11, 2016.

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53 620 **Discussion**

621 Risk-benefit Assessment

622 Neither intensification nor prolonging initial therapy has influenced long-term prognosis of SSNS in
623 terms of number of relapses and risk of frequent relapses [12–15]. MMF is effective in sustaining
624 remission in patients with frequently relapsing steroid-sensitive nephrotic syndrome [16, 21, 22].
625 Therefore we hypothesize that after initial remission is achieved the risk for immediate relapse will
626 not be increased in the experimental group. If a patient of the experimental group develops a relapse
627 under MMF therapy he or she will be given prednisone anyway for induction of remission; the overall
628 prognosis would therefore not be influenced. On the other hand, the patients in the experimental
629 group may have the potential to benefit significantly because of less glucocorticoid-associated
630 toxicity.

631 The most frequently observed side effects of MMF are gastrointestinal
632 symptoms such as nausea, vomiting, stomach pain and diarrhea and hematological symptoms such
633 as leukopenia, anemia and rarely thrombocytopenia and an enhanced susceptibility for
634 infections. In general, these side effects occur more frequently and have a higher clinical
635 significance, when MMF is administered in conjunction with other immunosuppressive
636 medication such as CSA or tacrolimus, as indicated after solid organ transplantation.

637 When MMF is administered as monotherapy, for example in patients with frequently relapsing
638 steroid-sensitive nephrotic syndrome, the frequency and severity of these side effects are
639 markedly lower [16–21]. Side effects will be systematically evaluated during the trial
640 visits.

641 In order to acknowledge recently reported adverse events (hypogammaglobinemia,
642 bronchiectasis, the risk of terato- and mutagenity) in patients after solid organ transplantation and
643 treated with MMF in conjunction with other immunosuppressive medications in the long-time run,
644 these adverse events are also monitored closely in the INTENT study, despite these events are very
645 unlikely to occur due to the short administration period of MMF (max. 11 weeks) and the age group
646 being tested in this trial.

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647 The oral formulation of MMF being a suspension allows exact and flexible dosing and reliable
648 administration even to small children.

651 **Cost-benefit analysis**

652 The costs for a treatment with mycophenolic acid for an average time of 74 days (84 days of initial
653 treatment minus an average of 10 days till remission) in a child with a body surface area of 0.8 m² in
654 Germany are approximately ten times higher than the standard treatment with prednisone (500 €
655 compared to 50 €). With the expected 250 new cases of childhood nephrotic syndrome per year this
656 would mean extra costs of about 110.000 € for the German health care system. On the other hand, it
657 has been shown that excessive weight gain during the initial steroid therapy in a significant subset
658 (47%) of patients after cessation of glucocorticoid therapy persisted and thus contributes to long-
659 term cardiovascular risk.[10, 11] These potential extra costs are hardly to be calculated but it seems
660 reasonable enough to avoid long-term effects of high dose prednisone treatment.

661 **Potential impact**

662 The current study continues the long-lasting tradition of prospective randomized trials on the initial
663 treatment of idiopathic nephrotic syndrome performed by the *GPN* (formerly *Arbeitsgemeinschaft*
664 *für Pädiatrische Nephrologie*).
665 This is the first trial worldwide that prospectively evaluates a steroid-reduced initial treatment
666 alternative that has the potential to reduce the number of side effects without lacking efficacy. If our
667 hypotheses turn out to be true, the experimental therapy has the potential to become the future
668 standard of care.

670 **Optimizing recruitment**

Our structure of numerous study centers covering entire Germany that collaborate with regional hospitals and practitioners should make most new manifestations of idiopathic nephrotic syndrome available to study evaluation.

Nevertheless patient recruitment currently stays behind schedule. One aspect to improve recruitment is initiation of further study centers especially in densely populated areas in Southern Germany. Other aspects are strengthening the motivation of collaborating partners to transfer patients, advertising the study in widely distributed journals, by personal contact via mail and phone and to introduce the study at all suitable annual conferences. If patient recruitment cannot be increased sufficiently by these measures the recruitment period has to be prolonged.

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682 **Dissemination**

The study results will be published in accordance with the CONSORT statement and SPIRIT guidelines.

Our findings will be submitted to major international pediatric nephrology and general pediatric conferences and submitted for publication in a high impact factor journal with open access.

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687 **Trial status**

The recruitment of the study started in October 2015.

As of June 12, 2018 a total of 156 children have been recruited into the study.

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691 **List of abbreviations**

| | | |
|-----|-----|--|
| 692 | AAP | American Academy of Pediatrics |
| 693 | AE | Adverse event |
| 694 | AMG | Arzneimittelgesetz (German Medicinal Products Act) |
| 695 | APN | Arbeitsgemeinschaft für Pädiatrische Nephrologie |

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| 3 | 696 | BMBF | Bundesministerium für Bildung und Forschung (German Federal Ministry of |
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| 5 | 697 | | Education and Research) |
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| 7 | 698 | BSA | Body surface area |
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| 11 | 700 | DSMB | Data safety monitoring board |
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| 13 | 701 | eCRF | Electronic case report form |
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| 15 | 702 | eGFR | Estimated glomerular filtration rate |
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| 17 | 703 | ESPED | Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland (German |
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| 19 | 704 | | registry of rare pediatric diseases) |
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| 21 | 705 | GCP | Good Clinical Practice |
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| 23 | 706 | GPN | Gesellschaft für Pädiatrische Nephrologie (Society of Pediatric Nephrology) |
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| 25 | 707 | ICH-GCP | International Council for Harmonisation of Technical Requirements for |
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| 27 | 708 | | Pharmaceuticals for Human Use harmonized tripartite guideline on Good Clinical |
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| 29 | 709 | | Practice |
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| 32 | 710 | IMBI | Institute of Medical Biometry and Informatics |
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| 34 | 711 | IMPDH | Inosine monophosphate dehydrogenase |
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| 36 | 712 | ITT | Intention-to-treat |
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| 38 | 713 | KDIGO | Kidney Disease Improving Global Outcomes |
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| 40 | 714 | MMF | Mycophenolate mofetil |
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| 42 | 715 | MPA | Mycophenolic acid |
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| 44 | 716 | MPG | Medizinproduktegesetz (Act on Medical Devices) |
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| 46 | 717 | PP | Per-protocol |
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| 48 | 718 | SAE | Severe adverse event |
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| 50 | 719 | SAP | Statistical analysis plan |
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| 52 | 720 | SOP | Standard Operating Procedure |
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| 54 | 721 | SSNS | Steroid-sensitive nephrotic syndrome |
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722 SUSAR Suspected unexpected severe adverse event

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724 **Declarations**

725 **Ethics approval and consent to participate**

726 Ethics approval of the INTENT study was granted by the ethics committee of the Medical Faculty of
727 the University of Heidelberg (AFmu-554/2014) on March 18, 2015. Informed consent will be/has
728 been obtained from all participants.

729

730 **Consent for publication**

731 Not applicable.

732

733 **Availability of data and material**

734 <http://www.intent-study.de>

735

736 **Competing interests**

737 RE, MRB, JD, AF, JG, DH, BH, PFH, BK, MJK, MK, SL, UQ and AS declare to have no competing
738 interests. BT and LTW have received research grants from Roche Pharma AG and Novartis AG.

739

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742 funding reference number 01KG1301).

743

744 **Authors contributions**

745 MRB, LTW, BT, JD, JG, DH, PFH, MJK, MK, UQ, AF, AS, RE designed the study. AS, MRB, RE, BT and
746 LTW will undertake data analyses. BK and SL gave advice in regulatory affairs and in realization of the

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3 747 study. RE, MRB, BT and LTW wrote the first draft of this manuscript, which has been critically revised
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5 748 by all co-authors. All authors have read and approved the final version of the manuscript.
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9 750 **Acknowledgements**

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11 751 Not applicable.
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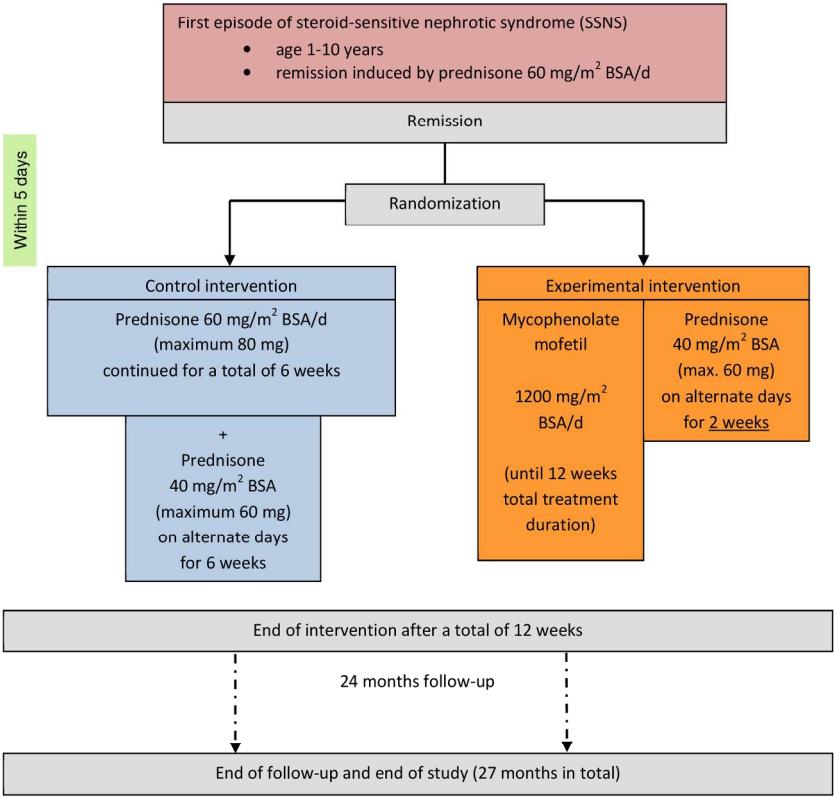
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55 813 **Legends to figure 1 and 2:**
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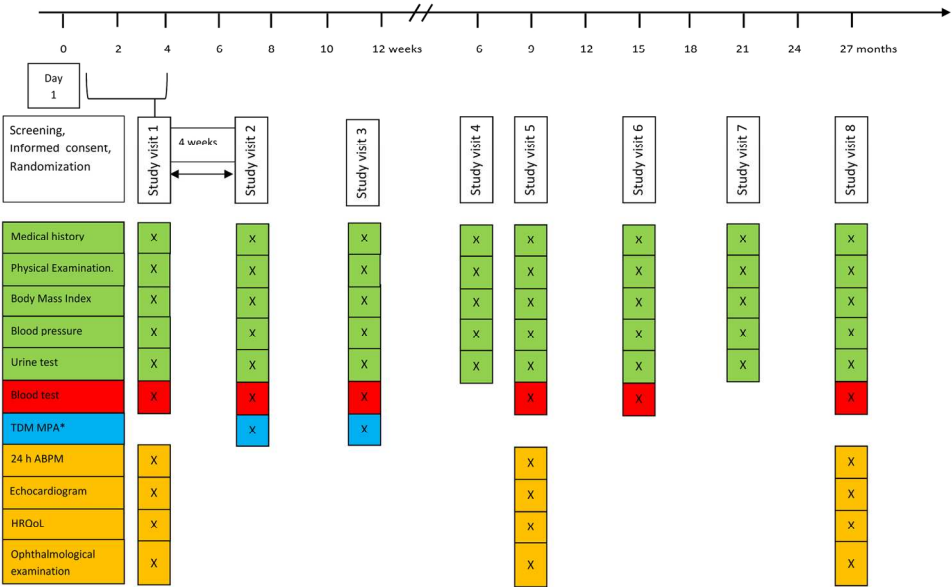
814 **Figure 1: Trial schema.** On alternate days = every second day, BSA = body surface area

815 **Figure 2: Study visit schedule.** TDM MPA = therapeutic drug monitoring of mycophenolic acid, ABPM
816 = ambulatory blood pressure monitoring, HRQoL = health related quality of life, *only in the
817 experimental group

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192x179mm (300 x 300 DPI)



160x107mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| Administrative information | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | ____1____ |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | ____5____ |
| | 2b | All items from the World Health Organization Trial Registration Data Set | ____-____ |
| Protocol version | 3 | Date and version identifier | _____ |
| Funding | 4 | Sources and types of financial, material, and other support | ____4____ |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | ____1-3____ |
| | 5b | Name and contact information for the trial sponsor | see study protocol |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | _____ |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | _____ |

Introduction

| | | | |
|--------------------------|----|---|-------------|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | ____6,7____ |
| | 6b | Explanation for choice of comparators | ____9____ |
| Objectives | 7 | Specific objectives or hypotheses | ____8____ |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | ____9____ |

Methods: Participants, interventions, and outcomes

| | | | |
|----------------------|-----|--|------------------------|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | ____10____ |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | ____10,11____ |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | ____13____ |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | __see study protocol__ |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | ____12____ |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | _____ |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | ____14-16____ |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | __Figure 2__ |

| | | | | |
|----|---|-----|--|--------------------------|
| 1 | | | | |
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| 3 | Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | _____16_____ |
| 4 | | | | |
| 5 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 10, 25 |
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| 8 | Methods: Assignment of interventions (for controlled trials) | | | |
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| 10 | Allocation: | | | |
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| 12 | Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | _____12_____ |
| 13 | | | | |
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| 17 | Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | _____12_____ |
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| 21 | Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | _____12_____ |
| 22 | | | | |
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| 24 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | not applicable |
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| 27 | | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | _____ |
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| 31 | Methods: Data collection, management, and analysis | | | |
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| 33 | Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | _____ |
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| 38 | | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | _see study protocol_____ |
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| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | _____21_____ |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | __17-19_____ |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | _____ |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 17-19 |
| Methods: Monitoring | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | __see study protocol_____ |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | _20_____ |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 20-21_____ |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | _see study protocol_____ |
| Ethics and dissemination | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | __27_____ |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | _see study protocol_____ |

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|----|-------------------------------|-----|---|-------------------------|
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| 3 | Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | _____12_____ |
| 4 | | | | |
| 5 | | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | _____ |
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| 8 | Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | _____ |
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| 11 | Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | ____27_____ |
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| 14 | Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | _____ - _____ |
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| 17 | Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | See study protocol_____ |
| 18 | | | | |
| 19 | Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | _____ - _____ |
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| 24 | | 31b | Authorship eligibility guidelines and any intended use of professional writers | _____ - _____ |
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| 26 | | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | ____27_____ |
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| 29 | Appendices | | | |
| 30 | | | | |
| 31 | Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | yes_____ |
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| 34 | Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | _____ |
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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BMJ Open

**Initial treatment of steroid-sensitive idiopathic nephrotic syndrome in children with mycophenolate mofetil vs. prednisone:
Protocol for a randomized, controlled, multicenter trial (INTENT Study)**

| | |
|---------------------------------|---|
| Journal: | BMJ Open |
| Manuscript ID | bmjopen-2018-024882.R1 |
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| Date Submitted by the Author: | 30-Aug-2018 |
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| Primary Subject Heading: | Paediatrics |

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| Secondary Subject Heading: | Renal medicine, Pharmacology and therapeutics |
| Keywords: | steroid-sensitive nephrotic syndrome, steroids, alternative treatment, mycophenolate mofetil |
| | |

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Manuscripts

For peer review only

1 Initial treatment of steroid-sensitive idiopathic nephrotic syndrome in children with mycophenolate

2 mofetil vs. prednisone:

3 Protocol for a randomized, controlled, multicenter trial (INTENT Study)

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5 Haffner⁴, Britta Höcker², Peter F. Hoyer⁵, Bärbel Kästner⁶, Markus J. Kemper⁷, Martin Konrad⁸, Steffen
6 Luntz⁶, Uwe Querfeld³, Anja Sander⁹, Burkhard Toenshoff^{2*}, Lutz T. Weber^{1*} on behalf of the
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84 *authors contributed equally to this work

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104 **Abstract**

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105 Introduction

106 Idiopathic nephrotic syndrome is the commonest glomerular disease in childhood with an incidence
107 of 1.8 cases per 100.000 children in Germany. The treatment of the first episode implies two aspects:
108 induction of remission and sustainment of remission. The recent KDIGO, American Academy of
109 Pediatrics (AAP) and German guidelines for the initial treatment of the first episode of a nephrotic
110 syndrome recommend a 12-week-course of prednisone. Even though being effective, this treatment
111 is associated with pronounced glucocorticoid-associated toxicity due to high-dose prednisone
112 administration over a prolonged period of time. The aim of the INTENT study is to show that an
113 alternative treatment regimen with mycophenolic acid is not inferior regarding sustainment of
114 remission but with lower toxicity compared to treatment with glucocorticoids only.

115 Methods and design

116 The study is designed as an open, randomized, controlled, multicenter trial. 340 children with a first
117 episode of steroid-sensitive nephrotic syndrome and achieved remission by a standard prednisone
118 regime will be enrolled in the trial and randomized to one of two treatment arms. The standard care
119 group will be treated with prednisone for a total of 12 weeks; in the experimental group the
120 treatment is switched to mycophenolate mofetil, also for a total of 12 weeks treatment duration. The
121 primary endpoint is the occurrence of a treated relapse within 24 months after completion of initial
122 treatment. This study is funded by the German Federal Ministry of Education and Research.

123 Ethics and dissemination

124 Ethics approval for this trial was granted by the ethics committee of the Medical Faculty of the
125 University of Heidelberg (AFmu-554/2014). The study results will be published in accordance with the
126 CONSORT statement and SPIRIT guidelines. Our findings will be submitted to major international
127 pediatric nephrology and general pediatric conferences and submitted for publication in a peer-
128 reviewed open access journal.

129

130 **Trial registration:** European Clinical Trials Database EudraCT No.: 2014-001991-76

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131 Date of registration: October 30, 2014

132 Deutsches Register Klinischer Studien – German clinical trials register

133 DRKS00006547

134 Date of registration: Februar 24, 2017

135

136

137 **Keywords:** mycophenolate mofetil; steroid-sensitive nephrotic syndrome, steroids,

138 alternative treatment

139

140 **Article summary**

141 **Strengths and limitations of this study**

- 142 • This is the first trial worldwide that prospectively evaluates a steroid-reduced initial
- 143 treatment alternative for childhood nephrotic syndrome
- 144 • This trial has the potential to reduce steroid-associated side effects without losing efficacy
- 145 • If our hypotheses turn out to be true, the experimental therapy has the potential to become
- 146 the future standard of care
- 147 • This is one of the few randomized, controlled, prospective, multicenter trials in pediatric
- 148 nephrology, but due to clinical and financial aspects the trial is not blinded

150 **Word count:** 5688 words

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156 **Introduction**

157

158 Idiopathic nephrotic syndrome in childhood

159

160 Clinical course and epidemiology

161 Idiopathic nephrotic syndrome in childhood, defined as the combination of heavy proteinuria
162 ($>40 \text{ mg/m}^2$ body surface area (BSA) per h) and hypalbuminemia ($<25 \text{ g/L}$), in general accompanied
163 by edema and hyperlipidemia, is a rare, relapsing disease with an incidence of 1.8 per 100.000
164 children below 16 years of age in Germany (German registry of rare pediatric diseases, ESPED 2005-
165 2006), resulting in an annual rate of 200-250 new patients.[1] The classification according to the four
166 following categories is important for diagnostics, treatment and prognosis of nephrotic syndrome in
167 childhood: etiology, age at onset, histology, response to glucocorticoids. The primary idiopathic
168 nephrotic syndrome with a typical onset at 1-10 years of age should be differentiated from
169 patients with secondary causes or patients with age at onset younger than one year (congenital
170 and infantile forms) or older than 10 years of age. Approximately 80% of the children with
171 idiopathic nephrotic syndrome have minimal change disease in renal biopsy and approximately 7%
172 focal segmental glomerulosclerosis. The most important prognostic factor is steroid-sensitivity
173 occurring in over 90% of the patients.

174

175 Treatment

176 The treatment of the first episode implies two aspects: induction of remission and sustainment
177 of remission. The *Gesellschaft für Pädiatrische Nephrologie (GPN)*, formerly known as
178 *Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)*, defined the standard
179 of care for children with nephrotic syndrome.[2–7] *The effectual guideline for the initial*
180 *treatment of the first episode of a nephrotic syndrome recommends in detail: 60 mg*
181 *prednisone/m² BSA per day (maximum 80 mg/day) for 6 weeks followed by alternate day prednisone*
182 *40 mg/m² BSA (maximum 60 mg/48 hours) for another 6 weeks.[8]*

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183 In case of steroid-sensitivity remission usually occurs within 7-14 days of
184 treatment; the overall duration of initial prednisone treatment is 12 weeks in order to sustain
185 remission. This regimen is associated with a relapse rate of 51% within 24 months after initial
186 prednisone
187 therapy, and a rate of frequent relapses (definition: relapses occur 4 or more times in any 12 month
188 period or 2 or more relapses within the first 6 months period after initial response) of 29% is
189 expected.

191 **Side effects of treatment**

192 Even though being effective, this treatment is associated with pronounced glucocorticoid associated
193 toxicity due to high-dose prednisone administration over a prolonged period of time.
194 The major side effects, which have been shown consistently in previous studies,[3, 4, 9]
195 comprise obesity, striae, hypertrichosis, cataract, glaucoma, arterial hypertension, psychological
196 disturbances, growth failure, disturbances in carbohydrate and lipid metabolism, osteopenia,
197 and avascular bone necrosis. Not all of these side effects are completely reversible after cessation of
198 steroid therapy. In one study for example, excessive gain of weight during initial steroid therapy
199 persisted in a significant subset (47%) of patients following cessation of glucocorticoid therapy.[10]
200 Obesity following cessation of glucocorticoid therapy was associated with
201 hyperlipidemia, which might enhance the cardiovascular risk of these patients in the long run.[11]
202 Other studies have shown that exposure to higher doses of glucocorticoids in the initial therapy leads
203 to more toxicity without prevention of future relapses.[12–15]

205 **Role of mycophenolate mofetil in the treatment of nephrotic syndrome in childhood**

206 Mycophenolate mofetil (MMF), the pro-drug of its active moiety mycophenolic acid (MPA), is a
207 potent, selective and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH),
208 the key enzyme of *de novo* purine synthesis in activated lymphocytes. MMF is

209 effective in sustaining remission in patients with frequently relapsing or glucocorticoid-dependent
210 nephrotic syndrome.
211 Four prospective studies in patients with frequently relapsing or glucocorticoid-dependent nephrotic
212 syndrome receiving a long-term therapy with MMF explored the possibility of withdrawing
213 prednisone, which was successful in >50% of patients without further relapses.[16–19]
214 In children with glucocorticoid-dependent nephrotic syndrome on MMF, Dorresteijn et al. reported
215 relapse rates of 25% after 6 months and 45% after 12 months, respectively.[20] In a phase II Bayesian
216 trial, Baudouin et al. confirmed the effect of MMF in reducing relapse rates and in sparing
217 glucocorticoids in children with glucocorticoid-dependent nephrotic syndrome.[21] A recent GPN
218 study on the maintenance of remission in children with frequently relapsing or steroid-dependent
219 nephrotic syndrome has shown that MMF in adequate exposure is as effective as cyclosporine A
220 (CSA) in sustaining remission without the burden of CSA-induced nephrotoxicity.[22]
221
222 So far, no studies with MMF for the initial treatment of the steroid-sensitive
223 nephrotic syndrome (SSNS) in children have been performed. However, it seems coherent to use the
224 efficacy of MMF also for sustaining remission in the initial treatment of SSNS and to benefit from its
225 lower toxicity compared to glucocorticoids.

227 Rationale

228 The initial treatment of the idiopathic nephrotic syndrome in children requires sufficient
229 immunosuppressive therapy, but should avoid toxicity, since the intensity of the initial treatment
230 does not influence the long-term course of the disease. For example, a GPN trial on the initial
231 treatment of nephrotic syndrome revealed no overall advantage of an intensified
232 immunosuppressive protocol adding CSA in terms of occurrence of relapses during a follow-up of 24
233 months.[5, 12, 13]

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Our hypothesized novel treatment protocol has the potential to reduce the burden of glucocorticoid-associated side effects and associated cardiovascular risk factors, if the novel protocol is not inferior to the standard therapy regarding sustainment of remission. If our hypothesis turns out to be true, this novel therapy has the potential to become the standard of care for the initial treatment of SSNS in children.

Methods/design

Aim

The main purpose of the study is to show that MMF in the initial treatment of SSNS in children is not inferior regarding maintenance of initial remission and subsequent relapse rate compared to the standard prednisone regimen.

Study design

This is a prospective, randomized, multicenter, controlled, open, parallel group phase III non-inferiority trial.

After initiation of the study, patients will be screened consecutively and eligible patients will be enrolled into the study at each center.

Each sites' principal investigator has to declare to the coordinating investigator/sponsor that he/she will conduct the study according to the protocol, ethical rules, and to provide the support as needed. To minimize a potential performance bias, this will be fixed in a contract prior to commencing the study. The clinical monitor will introduce the sites in detail to study procedures and documentation in advance.

Bias by potential influential factors will be addressed by inclusion as covariates into the statistical analysis. Independent clinical on-site monitoring to ensure patients safety and integrity of the clinical data in adherence to study protocol will focus on source data documentation, correctness of data, and adherence to study procedures, e.g. randomization

260 and treatment.

261 Based on the performed interventions and planned analysis blinding is not feasible to minimize
262 bias, because the interventions can easily be differentiated due to visible side
263 effects such as obesity, which is only expected in the standard care group. Furthermore, MMF is used
264 in liquid form as a suspension and prednisone as a tablet. However, the primary endpoint is based on
265 standardized diagnostic work-up results, i.e. objective criteria.

266 The duration of the study for each subject is expected to be 27 months (including 24 months
267 follow-up after intervention). (Figure 1 and Figure 2)

268

269 **Patient and public involvement**

270 Patients were not directly involved in the study development and design. Repeated discussions with
271 patient representatives beforehand showed one of their main wishes that is reduction of steroids in
272 the treatment of nephrotic syndrome.

273 We generated an information document for parents in form of a flyer that was distributed also to
274 patient initiatives. Spreading out information on the study shall improve recruitment. There is no
275 patient adviser involved in the conduct of the study, neither was the burden of the intervention
276 assessed by patients or their parents during study development.

277 Study results will be published open access. Patients and their representatives will be informed
278 through meetings and a brief summary of the results distributed by local investigators.

279

280 **Recruitment**

281 The study is conducted on a multicenter basis. The rarity of the disease requires a
282 nationwide recruitment. The planned 35 study centers are evenly distributed over
283 Germany. Each study center is coordinating a number of collaborating hospitals and practitioners
284 that will transfer eligible patients with primary onset steroid-sensitive nephrotic syndrome for

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3 285 screening, enrollment, randomization and study visits. 400 patients should be assessed for eligibility,
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5 286 340 subjects should be enrolled in the clinical study, i.e. 170 subjects per treatment group.
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9 288 **Inclusion criteria and exclusion criteria**
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11 289 ***Inclusion criteria***
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13 290 Subjects meeting all of the following criteria will be considered for admission to the study:
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15 291 - First episode of SSNS
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17 292 - *Remission induced by prednisone or prednisolone 60 mg/m² BSA (maximum 80 mg/day) per day*
18
19 293 *within 28 days*
20
21 294 - Male and female children aged ≥ 1 year and ≤ 10 years at beginning of the study (typical
22
23 295 age range of patients with SSNS)
24
25 296 - Ability of the persons having care and custody of the child to understand character
26
27 297 and individual consequences of clinical study
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29 298 - Written informed consent of the persons having care and custody of the child (must
30
31 299 be available before enrollment in the study)
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33 300
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35 301 ***Exclusion criteria***
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37 302 Subjects presenting with any of the following criteria will not be included in the study:
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39 303 - Secondary nephrotic syndrome
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41 304 - Estimated glomerular filtration rate (eGFR) <90 mL/min x 1.73 m² BSA
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43 305 - Ongoing treatment with systematically administered glucocorticoids or other
44
45 306 immunosuppressive drugs at time of first episode of nephrotic syndrome
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47 307 - Hemoglobin concentration of ≤90 g/L (SI unit)
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49 308 - Leucocyte count of ≤2.5 x 10⁹/L (SI unit)
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51 309 - Severe chronic gastrointestinal disease
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53 310 - History of hypersensitivity to MMF or to any drug with similar
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- 311 chemical structure or to any excipient present in the pharmaceutical form of
- 312 suspension of MMF (CellCept® suspension)
- 313 - Refusal of subject
- 314 - Participation in other clinical studies or observation period of competing studies

315

316 **Study medication**

317 The sponsor, i.e. the University Hospital Heidelberg, will provide the required study medication

318 (mycophenolate mofetil, CellCept® suspension). Careful records will be kept of the study medication

319 supplied to the centers and distributed to the patients.

320 Prednisone is used as standard therapy following the definition of the *GPN* (standard treatment) and

321 is prescribed as usual.

322

- 323 • Prednisone or prednisolone (control intervention)
- 324
- 325 • MMF is administered in liquid form (CellCept® suspension (Roche Registration Ltd.))
- 326 (experimental intervention)

327

328 **Adherence**

329 Adherence will be recorded by the patients' diary.

330

331 **Screening**

332 All patients who seem suitable for study participation and take part in the screening will receive a

333 screening number and will be registered in a screening log. Together with the center ID this will be

334 the unique identification number throughout the study.

335 Parents of children with initial episode of idiopathic nephrotic syndrome aged between 1 and 10

336 years and treated with standard regime (prednisone 60 mg/m² BSA per day) will be informed about

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the ongoing INTENT study. If the child fulfills the inclusion criteria the persons having care and custody of the child and the patient, if ≥ 6 years of age, will be formally elucidated about the INTENT study by the study center in a form understandable to him or her and asked for written assent/consent.

For checking the exclusion criteria concerning eGFR, leucocyte count and hemoglobin concentration the most recent lab values should be used; they should have been obtained no more than 28 days prior to visit 1.

Randomization

To achieve comparable intervention groups, patients will be allocated in a concealed fashion by means of randomization using a centralized web-based tool (www.randomizer.at). Randomization will be performed stratified by age groups (grouped: < 7 years of age, ≥ 7 years of age), because age is known to influence the occurrence of relapses. If the randomizer is not available in urgent cases the Institute of Medical Biometry and Informatics can be contacted and a biometrician or data manager will perform the randomization.

Intervention

Maximum duration of treatment is 12 weeks after first day of initial treatment of SSNS. (Figure 1)

Control intervention

- Prednisone, which is continued for a total of 6 weeks with the dosage of 60 mg/m^2 BSA/d (maximum 80 mg), is given twice per day or three times per day
- plus

363 • Prednisone, which is given for another total of 6 weeks with the dosage of 40 mg/m²
364 BSA (maximum 60 mg) on alternate days (every other day) in one dose in the
365 morning

367 Resorption of prednisone is independent of food intake.

369 **Experimental intervention**

- 370 • MMF is given in a dosage of 1200 mg/m² BSA/d as a
371 suspension (200 mg/mL) until 12 weeks total treatment duration. MMF is given twice a
372 day, i.e. every 12 hours (\pm one hour)
- 373 • The suspension of MMF is prepared in the study center (according to the
374 summary of product information)
- 375 • The persons having care and custody of the child are informed that MMF should be
376 given 30 minutes before or 60 minutes after food intake.
- 377 • For the first two weeks from randomization on, prednisone is given with the dosage
378 of 40 mg/m² BSA (maximum 60 mg) on alternate days (every other day) in one dose in
379 the morning.
- 380 • *At Visits 2 and 3 MPA-exposure is measured by a limited sampling strategy (blood samples are*
381 *obtained at time points 0, 1 and 2 hours after intake of MMF*

383 **Recording of primary endpoint**

384 Daily dipstick testing of urine (Albustix®) and documentation in a standardized diary by a person
385 having care and custody of the child is common current practice in the care of patients with
386 nephrotic syndrome in pediatric nephrology centers.

387 No guideline exists on whether standard relapse treatment with prednisone should be started
388 immediately when definition of relapse is fulfilled to avoid the associated complications of an

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5 390 proteinuria resolves spontaneously. Therefore, in the INTENT study a time period of up to 10 days is
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7 391 allowed for a possible spontaneous remission, before standard therapy for relapse is started.
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9 392 Treatment of a relapse has to be performed according to standard therapy of the *GPN* (prednisone
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11 393 60mg/m² BSA [max 80mg] per day until the urine is free of protein for 3 consecutive days, followed
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13 394 by alternate day prednisone 40mg/m² BSA [max 60mg] for 4 weeks). Relapses with and without
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15 395 treatment are documented in the eCRF.
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17 396 Treatment of frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome
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19 397 with other medications than prednisone is carried out according to center practice, because there is
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21 398 no internationally accepted guideline on this topic. The performed treatment with
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23 399 immunosuppressive agents such as CSA, tacrolimus, MMF, cyclophosphamide, rituximab, or
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25 400 levamisole is documented in the eCRF.
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28 401 After completion of the study, patients will be treated according to center practice.
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32 403 **Outcome measures**

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34 404 **Primary study endpoint**

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36 405 The primary efficacy endpoint is occurrence of a treated relapse within 24 months after completion
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38 406 of initial treatment. The rationale is that this endpoint was chosen in all previous studies on the initial
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40 407 treatment of SSNS in children and is also the primary endpoint in various meta-analyses on this
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42 408 topic.[3–5, 7, 8]

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45 409 Definition of relapse: Relapse is denoted by a reappearance of proteinuria for 3 consecutive days:

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47 410 Albustix® ≥2+ (first or second morning urine)

48
49 411 or

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51 412 urine protein/creatinine (Up/c) ratio ≥2 g/g (first or second morning urine)

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53 413 or

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55 414 urine protein excretion of ≥40mg/m² BSA/h (urine collection for minimum 12 hours)
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416 Relapses with and without treatment are documented. The primary endpoint is fulfilled by the first
417 treated relapse.

418

419 **Secondary endpoints**

420 Secondary endpoints are divided into five items:

421 1. Course of the disease as described by the following criteria

422 a. Time from remission to first relapse

423 b. Number of relapses during follow-up

424 c. Mean relapse rate per patient and year

425 d. Number of frequent relapsers

426 e. Time from remission to intensification of immunosuppressive treatment with other
427 drugs due to glucocorticoid-induced toxicity

428 f. Rate of patients who require more intense immunosuppressive treatment (e.g. CSA,
429 tacrolimus, MMF, cyclophosphamide, rituximab, or levamisole)

430 2. Glucocorticoid-associated toxicity:

431 a. Cumulative prednisone dose as mg/m²

432 b. As there is no validated score for glucocorticoid-induced toxicity, each item is
433 registered separately. At study visits 1-8, body mass index, blood pressure, and
434 growth will be checked for quantitative influence, striae, hypertrichosis, acne, and
435 psychological disturbances by yes or no for qualitative influence. Additionally, at
436 study visits 1, 5, and 8, patients will be checked for cataract and glaucoma (by yes or
437 no).

438 3. MMF-associated toxicity: At all visits, patients will be checked for known side effects of MMF,
439 especially diarrhea, blood cell count disturbance, and infections.

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- 440 4. Health-related quality of life, which may be impaired in children with nephrotic syndrome
- 441 will be measured with a validated questionnaire (DISABKIDS) at visits 1/5/8.
- 442 5. Days missing school attendance and days of hospitalization will be documented as a measure
- 443 for the impact of the disease on everyday life.

445 It is expected that the MMF-based regimen will avoid acute and long-term glucocorticoid-associated

446 toxicity and is therefore superior regarding the benefit/risk ratio. However, this will not be tested

447 confirmatorily, since there is no endpoint or score summarizing the different aspects of side effects.

450 **Statistical considerations**

451 ***Sample size calculation***

452 The sample size calculation is based on the primary efficacy endpoint “occurrence of a treated

453 relapse within 24 months after completion of the initial treatment”. In the literature varying

454 information is given regarding the relapse rate for the control group receiving standard prednisone

455 therapy. We have decided to assume a relapse rate of 51% according to Gipson et al.[8] The same

456 rate is expected for the experimental group. If the relapse rate in the experimental group accounts to

457 less than 15% above the relapse rate of the control group, this will be considered as clinically

458 irrelevant based upon clinical judgement. Therefore the margin is set to $\delta=0.15$. As the direction of

459 the difference to be established is known for non-inferiority studies and as - due to the rareness of

460 the disease and the related limited available number of patients - the study could otherwise not be

461 performed with sufficient power, a one-sided significance level of 5% is applied. Testing at a one-

462 sided significance level of $\alpha = 5\%$ and aspiring a power of 80%, a total of 272 patients (136 per group)

463 are required (calculations performed with ADDPLAN 6.0). To account for a 10% drop-out rate and

464 major protocol violations in a further 10%, 340 patients will be randomized.

Adherence/Rate of loss of follow up

The nephrotic syndrome in children is mostly an acutely presenting disease, and parents are very concerned about their child. With standard prednisone treatment we observe a high adherence to therapy. According to our previous experience in performing studies in pediatric nephrology we assume that a minimum of 85% of patients assessed for eligibility will be allocated to the study [4, 5, 22]. Due to the exclusive care of these patients in specialized pediatric nephrology centers we calculate with a loss of follow-up either due to drop-out or major protocol violation of maximum 20% which corresponds to our previous studies.[4, 5, 22] The recent study of the GPN, showing that MMF is efficacious in sustaining remission in children with frequently relapsing nephrotic syndrome, had only a drop-out rate of 4%. Therefore, for the entire study, we estimated 400 children with steroid-sensitive nephrotic syndrome to be assessed for eligibility, 340 to be allocated to study and 272 patients to be analyzed per protocol. However, in cases of premature withdrawal by a patient the persons having care and custody of this patient will be asked for informed consent so that routinely recorded data by the covering physician can be used for the INTENT study. In this manner as many data as possible is recorded for evaluation of treatments in this rare disease.

Analysis populations

The primary analysis will be performed for both the per-protocol population (PP) and the intention-to-treat population (ITT). The PP population comprises all patients, who were treated according to the randomized treatment as outlined in the protocol without major protocol violations (e.g., reduction of study medication of >50% or interruption of study medication of >3 days, violation of inclusion or exclusion criteria). The ITT population will comprise all patients randomized into the study. In this set, every patient is analyzed according to the group randomized into.

Since there may be patients who withdraw from the study after the treatment period or within the treatment period but consent to the analysis of routinely recorded data was given the inclusion of these patients into the ITT population will be decided case by case before database lock and defined

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3 492 when writing the statistical analysis plan (SAP). As appropriate, a third population will be defined for
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5 493 analysis of the primary and important secondary endpoints. How to deal with these patients and
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7 494 their data in detail depends on the time point of withdrawal and the amount and reliability of the
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9 495 routinely collected data.
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11 496 The safety set will comprise all patients who have received study medication at least once, and will
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13 497 allocate the patients to the treatment they actually received, regardless of randomization. Whether
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15 498 routinely collected data of patients who withdraw prematurely can be included herein depends on
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17 499 the reliability of the collected safety data.
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21 501 **Statistical methods**

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23 502 The non-inferiority of the experimental group vs. control group will be evaluated using the test
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25 503 according to Farrington and Manning. The one-sided significance level is set to 5%.
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28
29 505 The hypotheses to be assessed in the primary efficacy analysis are formulated as follows:

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31 506 $H_0: p_{\text{MMF}} - p_{\text{Prednisone}} \geq \delta$ ($\delta=0.15$, non-inferiority margin, see sample size calculation for
32
33 507 justification)

34
35 508 $H_1: p_{\text{MMF}} - p_{\text{Prednisone}} < \delta$, where p_* denotes the relapse rate in the respective group.
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39 510 Before database closure the assignment of patients to the PP population (patients with no major
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41 511 protocol violations) and the ITT population (as classified by the intent-to-treat principle) are defined
42
43 512 in the statistical analysis plan. The confirmatory analysis is performed for both the PP population and
44
45 513 the ITT population. This approach reflects the equal importance of both analysis sets in a non-
46
47 514 inferiority trial. For the PP analysis missing values for the primary endpoint are not expected. In the
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49 515 ITT population missing values will be replaced according to Higgins.[23] As appropriate, a third
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51 516 population will be defined to adequately incorporate routinely collected data of patients who
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53 517 withdraw prematurely but gave informed consent for usage of routinely collected data. Details on
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inclusion of such data into sensitivity analyses of primary and secondary endpoints will be defined in more detail in the SAP. In case of uncertainty regarding data quality and reliability these patients will only be analyzed descriptively.

Additionally, binary logistic regression models will be performed as sensitivity analysis for the intervention comparison of the relapse rates adjusting for age, gender, center (grouped), and for results of therapeutic drug monitoring (grouped) based on different populations (PP, ITT, with values of drop-outs set to worst case).

All secondary outcomes will be evaluated descriptively, using appropriate statistical methods based on the underlying distribution of the data. Descriptive p-values are reported together with 95% confidence intervals for the corresponding effects. Descriptive statistics for continuous parameters and scores include number of non-missing observations, mean, standard deviation, median, minimum and maximum, performed for treatment groups as well as subgroups and overall. The description of categorical variables (ordinal or nominal) includes the number and percentage of patients belonging to the relevant categories in the study population as well as to each treatment group.

Rates of adverse and serious adverse events will be calculated with 95% confidence intervals for treatment group comparisons.

Statistical methods are used to assess the quality of the data, homogeneity of treatment groups, endpoints and safety of the two intervention groups. Details of the statistical analysis will be fixed at the latest in the SAP to be prepared within the first year after start of patient recruitment. All persons taking part in the preparation of the SAP and possible later changes to it will only have access to blinded data to avoid introduction of bias.

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541 **Interim Analyses**

542 No interim analysis will be performed for the following reason: The recruitment phase is planned to
543 be 36 months. The primary endpoint is occurrence of treated relapse within 24 months after end of

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initial treatment. Therefore, information on the primary endpoint for a first portion of the study patients will be available not before end of the recruitment phase. For this reason, a group-sequential approach was not pursued. However, an independent data safety monitoring board (DSMB) will closely monitor the recruitment, the reported adverse events, the data quality of the study and the occurrence of potential early relapses during the intake of MMF, thus ensuring the ethical conduct of the study and protecting the safety interests of patients.

Adverse events

Adverse events (AEs) will be ascertained by the investigators using non-leading questions, noted as spontaneously reported by the patients to the medical staff or observed during any measurements on all study days. The observation period begins with the first administration of the Investigational Medicinal Product and ends with visit 4, (i.e. 6 months after day 1 [= first day of treatment with standard therapy]). The patient or his primary care physician should report any AE during the outpatient period via phone to the investigator. AEs will be documented in the patient file and in the electronic case report form (eCRF). All subjects who present AEs, whether considered associated with the use of the study medication or not, will be monitored by the responsible investigator to determine their outcome; this applies to withdrawals, too.

All serious adverse events (SAEs) and their relevance for the benefit/risk assessment of the study will be evaluated continuously during the study and for the final report.

All SAEs must be reported by the investigator to the Department of Pharmacovigilance at the Coordination Center for Clinical Trials (KKS) Heidelberg within 24 hours after the SAE becomes known using the "Serious Adverse Event" form.

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571 Suspected unexpected serious adverse events (SUSARs) are to be reported to the responsible ethics
572 committee, the competent authority and to all participating investigators within defined timelines,
573 i.e. they are subject to an expedited reporting.

574 All SAEs will be subject to a second assessment by a designated person or his deputy, who will be
575 independent from the reporting investigator.

576

577 **Data management**

578 ***Data management and quality assurance***

579 The investigator or a designated representative must enter all protocol-required information in the
580 eCRF. The eCRF should be completed as soon as possible after the information is collected,
581 preferably on the same day when a study subject is seen for an examination, treatment, or any other
582 study procedure. The reason for missing data should be provided. The investigator is responsible for
583 ensuring that all sections of the eCRF are completed correctly and that entries can be verified in
584 accordance with the source data. Any entry and correction in the Remote Data Entry System will be
585 documented automatically in an audit file.

586 Completeness, validity and plausibility of data will be checked in time of data entry (edit-checks) and
587 using validating programs, which will generate queries. The investigator or the designated
588 representatives are obliged to clarify or explain the queries. If no further corrections are to be made
589 in the database it will be closed and used for statistical analysis. All data management procedures
590 will be carried out on validated systems and according to the current Standard Operating Procedures
591 (SOPs) of the Institute of Medical Biometry and Informatics (IMBI) of the University of Heidelberg.

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593 **Ethical and Legal Aspects**

594 The procedures set out in this study protocol, pertaining to the conduct, evaluation, and
595 documentation of this study, are designed to ensure that all persons involved in the study abide by

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International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use harmonized tripartite guideline on Good Clinical Practice (ICH-GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki.

The study will be carried out in conformity with the ICH Topic E6, Guideline for Good Clinical Practice, including post Step 4 errata, September 1997, Directive 2001/20/EC (April 4, 2001), Commission Directive 2005/28/EC (April 8, 2005), National regulatory requirements/guidelines of the participating countries concerning Clinical Studies [e.g. federal drug law (AMG), GCP ordinance (GCP-Verordnung), Medical device law (MPG)], general national regulatory requirements, e.g. Bundesdatenschutzgesetz (BDSG).

Ethics committee approval

Ethical approval of the INTENT study was granted by the ethics committee of the Medical Faculty of the University of Heidelberg (AFmu-554/2014) on March 18, 2015. This approval has subsequently been confirmed by the local ethics committees of all participating centers.

The latest version of the trial protocol (version 5.0) was approved by the ethics committee on June 01, 2016.

Approval of the regulatory authorities

According to the German Federal law the study was approved by the Federal Institute of Drugs and Medical Devices on April 02, 2015 (reference number 61-3910-4040246). The latest version of the trial protocol (version 5.0) was approved by the Federal Institute of Drugs and Medical Devices on July 11, 2016.

Discussion

622 Risk-benefit Assessment

623 Neither intensification nor prolonging initial therapy has influenced long-term prognosis of SSNS in
624 terms of number of relapses and risk of frequent relapses [12–15]. MMF is effective in sustaining
625 remission in patients with frequently relapsing steroid-sensitive nephrotic syndrome [16, 21, 22].
626 Therefore we hypothesize that after initial remission is achieved the risk for immediate relapse will
627 not be increased in the experimental group. If a patient of the experimental group develops a relapse
628 under MMF therapy he or she will be given prednisone anyway for induction of remission; the overall
629 prognosis would therefore not be influenced. On the other hand, the patients in the experimental
630 group may have the potential to benefit significantly because of less glucocorticoid-associated
631 toxicity.

632 The most frequently observed side effects of MMF are gastrointestinal
633 symptoms such as nausea, vomiting, stomach pain and diarrhea and hematological symptoms such
634 as leukopenia, anemia and rarely thrombocytopenia and an enhanced susceptibility for
635 infections. In general, these side effects occur more frequently and have a higher clinical
636 significance, when MMF is administered in conjunction with other immunosuppressive
637 medication such as CSA or tacrolimus, as indicated after solid organ transplantation.

638 When MMF is administered as monotherapy, for example in patients with frequently relapsing
639 steroid-sensitive nephrotic syndrome, the frequency and severity of these side effects are
640 markedly lower [16–21]. Side effects will be systematically evaluated during the trial
641 visits.

642 In order to acknowledge recently reported adverse events (hypogammaglobinemia,
643 bronchiectasis, the risk of terato- and mutagenity) in patients after solid organ transplantation and
644 treated with MMF in conjunction with other immunosuppressive medications in the long-time run,
645 these adverse events are also monitored closely in the INTENT study, despite these events are very
646 unlikely to occur due to the short administration period of MMF (max. 11 weeks) and the age group
647 being tested in this trial.

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648 The oral formulation of MMF being a suspension allows exact and flexible dosing and reliable
649 administration even to small children.

652 **Cost-benefit analysis**

653 The costs for a treatment with mycophenolic acid for an average time of 74 days (84 days of initial
654 treatment minus an average of 10 days till remission) in a child with a body surface area of 0.8 m² in
655 Germany are approximately ten times higher than the standard treatment with prednisone (500 €
656 compared to 50 €). With the expected 250 new cases of childhood nephrotic syndrome per year this
657 would mean extra costs of about 110.000 € for the German health care system. On the other hand, it
658 has been shown that excessive weight gain during the initial steroid therapy in a significant subset
659 (47%) of patients after cessation of glucocorticoid therapy persisted and thus contributes to long-
660 term cardiovascular risk.[10, 11] These potential extra costs are hardly to be calculated but it seems
661 reasonable enough to avoid long-term effects of high dose prednisone treatment.

662 **Potential impact**

663 The current study continues the long-lasting tradition of prospective randomized trials on the initial
664 treatment of idiopathic nephrotic syndrome performed by the *GPN* (formerly *Arbeitsgemeinschaft*
665 *für Pädiatrische Nephrologie*).
666 This is the first trial worldwide that prospectively evaluates a steroid-reduced initial treatment
667 alternative that has the potential to reduce the number of side effects without lacking efficacy. If our
668 hypotheses turn out to be true, the experimental therapy has the potential to become the future
669 standard of care.

671 **Optimizing recruitment**

Our structure of numerous study centers covering entire Germany that collaborate with regional hospitals and practitioners should make most new manifestations of idiopathic nephrotic syndrome available to study evaluation.

Nevertheless patient recruitment currently stays behind schedule. One aspect to improve recruitment is initiation of further study centers especially in densely populated areas in Southern Germany. Other aspects are strengthening the motivation of collaborating partners to transfer patients, advertising the study in widely distributed journals, by personal contact via mail and phone and to introduce the study at all suitable annual conferences. If patient recruitment cannot be increased sufficiently by these measures the recruitment period has to be prolonged.

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683 **Dissemination**

The study results will be published in accordance with the CONSORT statement and SPIRIT guidelines.

Our findings will be submitted to major international pediatric nephrology and general pediatric conferences and submitted for publication in a high impact factor journal with open access.

687

688 **Trial status**

The recruitment of the study started in October 2015.

As of June 12, 2018 a total of 156 children have been recruited into the study.

691

692 **List of abbreviations**

| | | |
|-----|-----|--|
| 693 | AAP | American Academy of Pediatrics |
| 694 | AE | Adverse event |
| 695 | AMG | Arzneimittelgesetz (German Medicinal Products Act) |
| 696 | APN | Arbeitsgemeinschaft für Pädiatrische Nephrologie |

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| 1 | | | |
| 2 | | | |
| 3 | 697 | BMBF | Bundesministerium für Bildung und Forschung (German Federal Ministry of |
| 4 | | | |
| 5 | 698 | | Education and Research) |
| 6 | | | |
| 7 | 699 | BSA | Body surface area |
| 8 | | | |
| 9 | 700 | CSA | Cyclosporine A |
| 10 | | | |
| 11 | 701 | DSMB | Data safety monitoring board |
| 12 | | | |
| 13 | 702 | eCRF | Electronic case report form |
| 14 | | | |
| 15 | 703 | eGFR | Estimated glomerular filtration rate |
| 16 | | | |
| 17 | 704 | ESPED | Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland (German |
| 18 | | | |
| 19 | 705 | | registry of rare pediatric diseases) |
| 20 | | | |
| 21 | 706 | GCP | Good Clinical Practice |
| 22 | | | |
| 23 | 707 | GPN | Gesellschaft für Pädiatrische Nephrologie (Society of Pediatric Nephrology) |
| 24 | | | |
| 25 | 708 | ICH-GCP | International Council for Harmonisation of Technical Requirements for |
| 26 | | | |
| 27 | 709 | | Pharmaceuticals for Human Use harmonized tripartite guideline on Good Clinical |
| 28 | | | |
| 29 | 710 | | Practice |
| 30 | | | |
| 31 | | | |
| 32 | 711 | IMBI | Institute of Medical Biometry and Informatics |
| 33 | | | |
| 34 | 712 | IMPDH | Inosine monophosphate dehydrogenase |
| 35 | | | |
| 36 | 713 | ITT | Intention-to-treat |
| 37 | | | |
| 38 | 714 | KDIGO | Kidney Disease Improving Global Outcomes |
| 39 | | | |
| 40 | 715 | MMF | Mycophenolate mofetil |
| 41 | | | |
| 42 | 716 | MPA | Mycophenolic acid |
| 43 | | | |
| 44 | 717 | MPG | Medizinproduktegesetz (Act on Medical Devices) |
| 45 | | | |
| 46 | 718 | PP | Per-protocol |
| 47 | | | |
| 48 | 719 | SAE | Severe adverse event |
| 49 | | | |
| 50 | | | |
| 51 | 720 | SAP | Statistical analysis plan |
| 52 | | | |
| 53 | 721 | SOP | Standard Operating Procedure |
| 54 | | | |
| 55 | 722 | SSNS | Steroid-sensitive nephrotic syndrome |
| 56 | | | |
| 57 | | | |
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723 SUSAR Suspected unexpected severe adverse event

724

725 **Declarations**

726 **Ethics approval and consent to participate**

727 Ethics approval of the INTENT study was granted by the ethics committee of the Medical Faculty of
728 the University of Heidelberg (AFmu-554/2014) on March 18, 2015. Informed consent will be/has
729 been obtained from all participants.

730

731 **Consent for publication**

732 Not applicable.

733

734 **Availability of data and material**

735 <http://www.intent-study.de>

736

737 **Competing interests**

738 RE, MRB, JD, AF, JG, DH, BH, PFH, BK, MJK, MK, SL, UQ and AS declare to have no competing
739 interests. BT and LTW have received research grants from Roche Pharma AG and Novartis AG.

740

741 **Funding**

742 The INTENT study is funded by the German Federal Ministry of Education and Research (BMBF,
743 funding reference number 01KG1301).

744

745 **Authors contributions**

746 MRB, LTW, BT, JD, JG, DH, BH, PFH, MJK, MK, UQ, AF, AS, RE designed the study. AS, MRB, RE, BT and
747 LTW will undertake data analyses. BK and SL gave advice in regulatory affairs and in realization of the

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study. RE, MRB, BT and LTW wrote the first draft of this manuscript, which has been critically revised by all co-authors. All authors have read and approved the final version of the manuscript.

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Not applicable.

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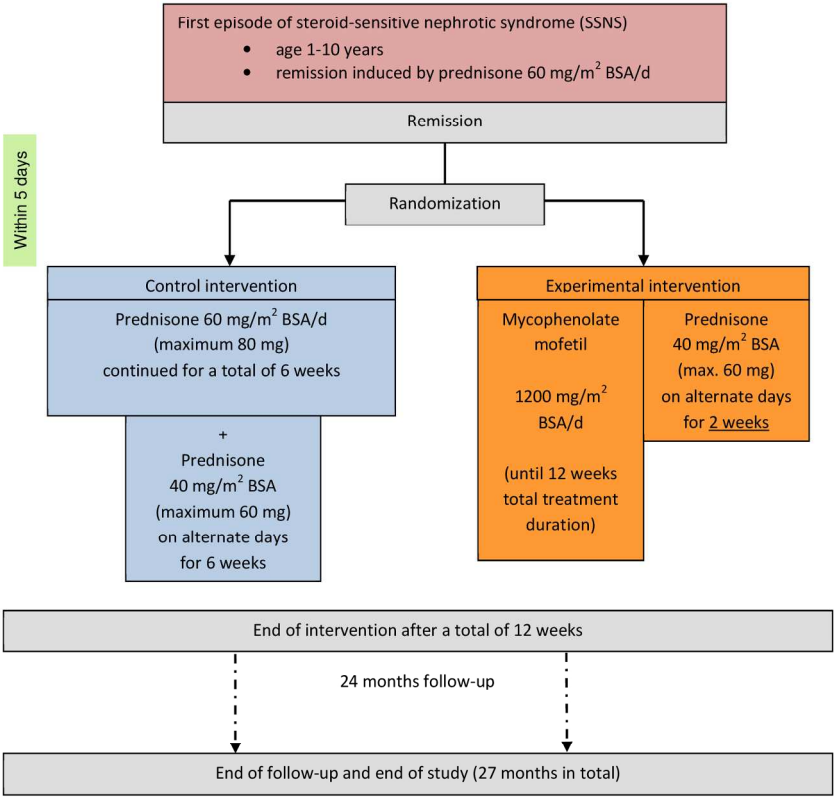
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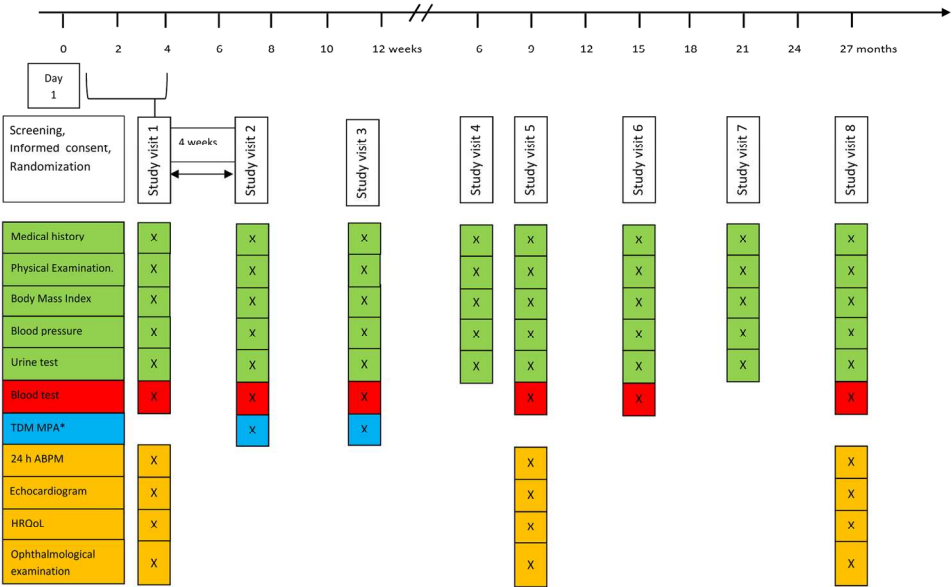
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55 814 **Legends to figure 1 and 2:**

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57 815 **Figure 1: Trial schema.** On alternate days = every second day, BSA = body surface area

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3 816 **Figure 2: Study visit schedule.** TDM MPA = therapeutic drug monitoring of mycophenolic acid, ABPM
4 817 = ambulatory blood pressure monitoring, HRQoL = health related quality of life, *only in the
5 818 experimental group
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| Administrative information | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | ____1____ |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | ____5____ |
| | 2b | All items from the World Health Organization Trial Registration Data Set | ____-____ |
| Protocol version | 3 | Date and version identifier | _____ |
| Funding | 4 | Sources and types of financial, material, and other support | ____4____ |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | ____1-3____ |
| | 5b | Name and contact information for the trial sponsor | see study protocol |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | _____ |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | _____ |

Introduction

| | | | |
|--------------------------|----|---|-------------|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | ____6,7____ |
| | 6b | Explanation for choice of comparators | ____9____ |
| Objectives | 7 | Specific objectives or hypotheses | ____8____ |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | ____9____ |

Methods: Participants, interventions, and outcomes

| | | | |
|----------------------|-----|--|------------------------|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | ____10____ |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | ____10,11____ |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | ____13____ |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | __see study protocol__ |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | ____12____ |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | _____ |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | ____14-16____ |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | __Figure 2__ |

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| 1 | | | | |
| 2 | | | | |
| 3 | Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | _____16_____ |
| 4 | | | | |
| 5 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 10, 25 |
| 6 | | | | |
| 7 | | | | |
| 8 | Methods: Assignment of interventions (for controlled trials) | | | |
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| 10 | Allocation: | | | |
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| 12 | Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | _____12_____ |
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| 17 | Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | _____12_____ |
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| 21 | Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | _____12_____ |
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| 24 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | not applicable |
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| 27 | | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | _____ |
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| 31 | Methods: Data collection, management, and analysis | | | |
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| 33 | Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | _____ |
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| 38 | | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | _see study protocol_____ |
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| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | _____21_____ |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | __17-19_____ |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | _____ |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 17-19 |
| Methods: Monitoring | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | __see study protocol_____ |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | _20_____ |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 20-21_____ |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | _see study protocol_____ |
| Ethics and dissemination | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | __27_____ |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | _see study protocol_____ |

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| 1 | | | | |
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| 3 | Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | _____12_____ |
| 4 | | | | |
| 5 | | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | _____ |
| 6 | | | | |
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| 8 | Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | _____ |
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| 10 | | | | |
| 11 | Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | ____27_____ |
| 12 | | | | |
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| 14 | Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | _____ - _____ |
| 15 | | | | |
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| 17 | Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | See study protocol_____ |
| 18 | | | | |
| 19 | Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | _____ - _____ |
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| 24 | | 31b | Authorship eligibility guidelines and any intended use of professional writers | _____ - _____ |
| 25 | | | | |
| 26 | | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | ____27_____ |
| 27 | | | | |
| 28 | | | | |
| 29 | Appendices | | | |
| 30 | | | | |
| 31 | Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | yes_____ |
| 32 | | | | |
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| 34 | Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | _____ |
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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